UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/943,664	08/30/2001	David Botstein	P2548P1C8	2448

7590 07/10/2008

BRINKS HOFER GILSON & LIONE
P.O. BOX 10395
CHICAGO, IL 60610

EXAMINER	
SAOUD, CHRISTINE J	
ART UNIT	PAPER NUMBER
1647	
MAIL DATE	DELIVERY MODE
07/10/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/943,664	BOTSTEIN ET AL.	
	Examiner	Art Unit	
	Christine J. Saoud	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Claims 1-26 and 35-36 have been canceled and claims 27-34 are currently pending in the response filed 25 February 2008. No claim amendments were filed with this response.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

Applicant's arguments filed 25 February 2008 have been fully considered but they are not deemed to be persuasive.

Claim Rejections - 35 USC §§ 101 and 112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-34 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Claims 27-34 remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons of record, one skilled in the art clearly would not know how to use the claimed invention.

The basis for these rejections is set forth in the previous Office actions of March 24, 2003, Sept. 24, 2003, March 17, 2005, Sept. 20, 2005, January 24, 2005, and March 7, 2007.

To review prosecution briefly, the Examiner has made a *prima facie* case that the mild amount of gene amplification (approximately 2 fold to 4 fold) of nucleic acids encoding the claimed protein are not indicative of an increased amount of mRNA or protein. It is noted that the data are drawn only to the comparison of genomic DNA. There is no disclosure of mRNA levels. Thus, the issue here is not whether the expression levels based upon DNA were significantly different in the tested tumors, but rather whether this data makes it more likely than not that the protein encoded by the gene is overexpressed.

Applicant argues at page 4 of the response that patent 7,208,308 has similar claims supported by the same utility based on similar data to that of the instant application. However, Applicant must remember that each application is examined on its own merits. A review of the '308 patent does not indicate a clear reason for allowance, so the rejection may have been withdrawn based on a determination that the polypeptide was a serine protease rather than for any reason related to the gene amplification data in the specification. Furthermore, the facts in the prosecution of the

‘308 patent are distinct from those in the instant application because the invention of the ‘308 patent is not the same invention that is claimed in the instant application. To conclude that the ‘308 patent was issued based on the gene amplification assay of Example 92 is misplaced since the record does not reflect this. Therefore, the issuance of the '308 patent is not persuasive evidence that the present claims are supported by a specific substantial and credible utility because the protein of the '308 patent is not the same, similar or related invention to the claimed invention in the instant application.

At pages 5-7 of the response, Applicant asserts that US Pat. No. 7,276,577 is evidence of utility. However, again, Applicant must note that each application is examined on its own merits. The claimed invention in the ‘577 patent is not the same protein claimed in the instant application. Lastly, the fact pattern in the prosecution of the ‘577 patent is distinct from that in the instant application because the ‘577 patent was allowed based on microarray data of mRNA. The issue in the instant application is that gene amplification (approximately 2 fold to 4 fold) of nucleic acids encoding the claimed protein are not indicative of an increased amount of mRNA or protein and the instant specification provides no disclosure of mRNA levels. Therefore, the fact pattern of the ‘577 is distinct from that of the instant application and no conclusions can be drawn from the issuance of the ‘577 patent related to the instant application.

Beginning at page 7 of the response, Applicant reviews Example 28, and refers to the Goddard declaration as establishing that an amplification of at least 2-fold is significant and indicative of a cancer diagnostic marker. The Goddard declaration under 37 CFR 1.132 filed 24 June 2003 is insufficient to overcome the rejection of claims 27-

34 based upon 35 U.S.C. §§ 101 and 112, first paragraph, as set forth in the previous Office actions for the following reasons. In assessing the weight to be given expert testimony, the Examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant situation, the nature of the fact sought to be established is whether or not a 2 to 6-fold amplification of the gene encoding PRO347 in 13 lung tumors and a 2 to 8-fold amplification of the gene encoding PRO347 in 9 colon tumors is significant. The significance can be questioned based on the absence of factual support for the expert's opinion. In the instant case, the facts are that while 9 colon tumors showed increased gene amplification, 8 colon tumor samples did not. Furthermore, the control used in the instant application was not a matched non-tumor sample but rather was a pooled DNA sample from blood of healthy subjects. The art uses matched tissue samples (see Pennica et al., Konopka et al.). This art, as well as the Sen, Hittelman, Godbout et al., and Li et al. references cited above, constitute strong opposing evidence as to whether or not the claimed polypeptides have utility and enablement based on a presumption of overexpression in view of gene amplification data. Finally, while the Goddard declaration speaks to the utility and enablement of genes, it does not speak to whether or not the encoded proteins are also found at

increased levels in cancerous tissues. Since the claims under examination are directed polypeptides, not genes, this question is critical.

At page 8 of the response, Applicant asserts that there is no requirement that the claimed PRO347 polypeptide identify all types and cases of colon cancer, but rather that the asserted utility be more likely than not. Applicant also argues that the data reported in Table 9 demonstrates that amplification of PRO347 more likely than not is useful as a marker for the diagnosis of cancer. Applicant's arguments have been fully considered, but are not persuasive. The data presented in Table 9 is not protein expression data, but rather amplification of genomic DNA and the record is clear that one cannot predict overexpression of proteins from genomic DNA. Therefore, Table 9 alone does not support a specific, substantial and credible utility for the claimed polypeptides.

On page 6 of the response, Applicants list 16 patents and assert that the PTO has acknowledged that on more than one occasion the asserted utility has been determined to be sufficient, and that the instant application relies on similar data. However, upon examination of those 16 applications, the data is not similar. In those 16 patents the asserted utility was based upon microarray data, which showed overexpression of mRNA in certain cancers, and in which is was determined that expression of mRNA correlates with expression of protein. However, the data in the instant application is amplification of genomic DNA, and as discussed in previous office actions it is not predictable that amplification of genomic DNA results in over-expression of mRNA.

At page 8 of the response, Applicant addresses the Hittleman reference and asserts that amplification of PRO347 was confirmed by framework mapping, which was used to control for aneuploidy. However, even if the data had been corrected for aneuploidy and a proper control had been used, the data have no bearing on the utility of the claimed PRO347 *polypeptides*. In order for PRO347 polypeptides to be overexpressed in tumors, amplified genomic DNA would have to correlate with increased mRNA levels and increased polypeptide levels. No data regarding PRO347 mRNA or PRO347 polypeptide levels in lung tumors have been brought forth on the record. The art discloses that a correlation between genomic DNA levels and mRNA levels cannot be presumed, nor can any correlation between genomic DNA levels and polypeptide levels.

Applicant argues at page 9 of the response that that ample evidence has been provided to show that, in general, if a gene is amplified in cancer, it is more likely than not that the corresponding mRNA and encoded polypeptide are also expressed at an elevated level. Applicant refers to Orntoft et al., Hyman et al. and Pollack et al. as teaching that, in general, gene amplification increases mRNA expression. Applicant asserts that Orntoft et al found that in general chromosomal areas with more than 2-fold gain of DAN showed a corresponding increase in mRNA transcripts and that Hyman et al. found that there was evidence of a prominent global influence of copy number changes on gene expression levels. Applicant asserts that Pollack et al. teach that a 2-fold change in DNA copy number was associated with a corresponding 1.5-fold change in mRNA levels.

These arguments have been fully considered but are not found to be persuasive. Orntoft et al. looked at increased DNA content over large regions of chromosomes and compared that to mRNA and polypeptide levels from the chromosomal region (see for example, p 44, last paragraph of col. 1). Their approach to investigating gene copy number was termed CGH. Orntoft et al. do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. The instant specification reports data regarding amplification of individual genes, which may or may not be in a chromosomal region which is highly amplified. Orntoft et al. concentrated on regions of chromosomes with clusters of chromosomal material containing strong gains, but it is not known whether PRO347 is in a gene cluster in a region of a chromosome that is highly amplified, which is pertinent because Orntoft et al. only provide information about genes in clusters (large chromosomal regions). The data of Orntoft et al. are not from looking at a 1:1 correspondence of genomic DNA and the mRNA which is transcribed from it. If PRO347 is not part of a cluster showing strong gains, then the findings of Orntoft et al. are not applicable. Because no such information was disclosed for PRO347, Orntoft et al. does not support Applicant's position. Ornoft et al. go on to say that detection was very limited.

While Hyman et al. and Pollack et al. combined CGH with microarray analysis, the results do not support a conclusion that the skilled artisan would reasonably expect amplified genomic DNA to correspond with overexpression of encoded protein. Hyman et al. used CGH in combination with cDNA microarray analysis. Less than half (44%) of *highly* amplified genes showed mRNA overexpression, and 10.5% of highly

overexpressed transcripts had amplified genes (p. 6242, col. 1, third full paragraph). Thus, even at the level of high amplification and high overexpression, the two do not usually correlate. Polypeptide levels were not investigated. Further, Hyman et al. state that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributed to gene amplification (col. 1, middle, p. 6244). This proportion was about 2% of the total. The Examiner maintains that 2% does not provide a reasonably expectation that the amplification of PRO347 would be correlated with elevated levels of mRNA, much less polypeptide. Since Hyman et al. found that less than half of the amplified genes were overexpressed at the mRNA level, the references supports the basis of the rejections that it is more likely than not that gene amplification fails to correlate with increased mRNA/polypeptide levels. Therefore, Hyman et al. also do not support utility of the claimed polypeptides. Pollack et al. concentrated on large chromosome regions showing high amplification (p. 12965). Pollack et al. did not investigate polypeptide levels. Pollack et al. also noted contradictory results found by another research group, Platzer et al., who found a poor correlation between DNA amplification and overexpression (p. 12967, col. 2, 7 lines from bottom). Pollack et al. noted that, “Alternatively, the contrasting findings for amplified genes may represent real biological differences between breast and metastatic colon tumors; resolution of this issue will require further studies” (p. 12968, end of first paragraph). This leads again to the issue of unpredictability, particularly when gene amplification of the instant PRO347 gene has been identified in lung and colon cancer instead of breast tumors.

At page 10 of the response, Applicant addresses the Scott Declaration. The Scott declaration under 37 CFR 1.132 filed 16 November 2006 is insufficient to overcome the rejection of the claims based upon 35 U.S.C. §§ 101 and 112, first paragraph for the following reasons. In assessing the weight to be given expert testimony, the Examiner may properly consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant case, (1) the nature of the fact sought to be established is whether or not gene amplification levels are predictive of polypeptide levels in a sample. (2) The opposing evidence, cited by the examiner, is considerably strong. (3) Dr. Scott does not appear to have an interest in the outcome of the case. (4) Finally, the Dr. Scott does not base his opinion on any particular facts other than his own considerable experience in the field. Affidavits or declarations are provided as evidence and must set forth facts, not merely conclusions. In re Pike and Morris, 84 USPQ 235 (CCPA 1949). While the declaration constitutes evidence that must be considered, the nature of the fact sought be established is not addressed by the Scott Declaration. The data presented in the instant specification is based on gene amplification, not on micro array, which is the subject of the Scott Declaration. Thus, consideration of the preponderance of the totality of the evidence indicates that the rejections should be maintained.

At pages 11-12 of the response, Applicant argues that the Godbout reference does not apply to PRO347 because amplification of PRO347 was confirmed by epicenter mapping and that one of ordinary skill in the art would conclude that PRO347 is not a co-amplified gene but rather an amplified gene.

Applicants' arguments have been fully considered but are not deemed persuasive. Godbout et al. (1998, J. Biol. Chem. 273(33):21161-8) speak to general lack of correlation between gene amplification and mRNA/protein overexpression. The abstract of Godbout teaches "The DEAD box gene, DDX1, is a putative RNA helicase that is co-amplified with MYCN in a subset of retinoblastoma (RB) and neuroblastoma (NB) tumors and cell lines. ***Although gene amplification usually involves hundreds to thousands of kilobase pairs of DNA, a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified***." (emphasis added). The protein encoded by the DDX gene *had been characterized* as being a putative RNA helicase, a type of enzyme that *would be expected to confer a selective advantage* to the cells in which it (the DDX gene) was amplified. On page 21167, right column, first full paragraph, Godbout et al. state ***"It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell*** (48, 49). For example, although ERBA is closely linked to ERBB2 in breast cancer and both genes are commonly amplified in these tumors, ERBA is not overexpressed (48). Similarly, three genes mapping to 12q13-14 (CDK4, SAS and MDM2) are overexpressed in a high percentage of malignant gliomas showing amplification of this chromosomal region,

while other genes mapping to this region (GADD153, GL1, and A2MR) are rarely overexpressed in gene-amplified malignant gliomas (50, 51). The first three genes are probably the main targets of the amplification process, while the latter three genes are probably incidentally included in the amplicons." (emphasis added). There is no evidence in the instant application that PRO347 confers any growth advantage to a cell, and thus it cannot be presumed that the protein is overexpressed because the genomic DNA including the gene being studied gene is amplified.

At pages 12-13 of the response, Applicant addresses the Pennica, Konopka and Li references and assert that the teachings of these references do not outweigh the evidence relied on by Applicant. Applicant argues that the teachings of Konopka and Pennica cannot support a general conclusion regarding correlation between gene amplification and mRNA or protein levels. Applicant further argues that the Pennica reference teaches that WISP-1 gene amplification and RNA expression levels showed a significant positive correlation, that WISP-3 was amplified and overexpressed, and that although WISP-2 gene amplification and and RNA expression seemed to be inversely related, Pennica suggests that this result might be inaccurate and this result should be disregarded.

These arguments have been fully considered but is not found to be persuasive. Both Pennica et al. and Konopka et al. are relevant even though they are not reviews of gene amplification for genes in general, because they show a lack of correlation between gene amplification and gene product overexpression for particular genes. The instant case also concerns a single gene. Pennica et al. showed that 2/3 WISP gene

levels did not correlate with mRNA levels. Konopka et al. showed that protein levels for the *abl* gene were due to variation in mRNA levels not gene amplification. Moreover, the rejection is based on more evidence than just Pennica et al. and Konopka et al. (see, for example, Godbout et al. and Li et al, discussed previously). The evidence of record indicates that (1) gene amplification does not reliably correlate with increased mRNA levels (Pennica et al., Konopka et al.), and (2) no evidence has been brought forth regarding levels of PRO347 mRNA or polypeptide levels in cancerous tissue. Finally, Pennica et al. provide evidence that closely related WISP genes show unpredictable gene amplification, mRNA and polypeptide levels. As discussed in the rejections above, these references are pertinent to the lack of reasonable expectation that for any given gene the level of gene copy number will correlate with protein expression.

Applicant argues at page 13 of the response that Li is not persuasive evidence in the context of the present invention because of framework and epicenter mapping analyses as well as the high rates of observed amplification for the PRO347 gene. Applicant's arguments have been fully considered, but are not persuasive. Li et al. used a functional approach that integrated simultaneous genomic and transcript microarray, proteomics, and tissue microarray analyses to directly identify putative oncogenes in lung adenocarcinoma. On page 2633, right column, Li et al. state: "***In our study, 68.8% of the genes showing over-representation in the genome did not show elevated transcript levels***, implying that at least some of these genes are 'passenger' genes that are concurrently amplified because of their location with respect to

amplicons but *lack biological relevance in terms of the development of lung adenocarcinoma*." Since more than half of the amplified genes were not overexpressed, Li et al. constitutes strong evidence that ***it is more likely than not that gene amplification does NOT correlate with increased protein levels***, absent evidence that the protein has biological relevance in cancer. There is no such evidence for PRO347.

At page 14 of the response, Applicant points to Appeal No. 2006-1469 and cites the Board as saying "there is a strong correlation between mRNA levels and protein expression". This decision is noted, but is not relevant to the facts of the instant application with regard to PRO347 because the evidence that is being relied upon relates to gene amplification and not mRNA levels from a microarray and Applicant has *not* established a showing that it is more likely than not that gene amplificaiton correlates with increased protein levels. The Office maintains its position based on the cited art, as discussed in the previous office actions and in above. Accordingly, the Examiner maintains the conclusion that it is more likely than not that the PRO347 protein would *not* be expected to be found in increased amounts in the cells tested by applicants, and thus has no readily available utility as a cancer diagnostic.

Applicant's statements regarding the rejection under 112/1st paragraph relate back to the rejection under 101, which have been addressed and answered above.

Conclusion

4. No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine J. Saoud whose telephone number is 571-272-0891. The examiner can normally be reached on Monday-Friday, 6AM-2PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine J Saoud/
Primary Examiner, Art Unit 1647

***